EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Division

# Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

## Zebinix

eslicarbazepine acetate

Procedure no: EMEA/H/C/000988/P46/026.1

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# 1. Introduction

This Post Authorisation Measure (PAM) submission concerns the extended submission of a clinical study - BIA-2093-211/EXT - to evaluate the safety profile of eslicarbazepine acetate (ESL) when used for 1 year by infants as well as to perform exploratory efficacy analyses in this population. Subjects eligible for this study were those infants who completed Study BIA-2093-211.

With PAM in October 2020 BIAL - Portela & Cª S.A. (Bial) submitted final study results and report related to paediatric population in line with Article 46 of paediatric regulation 1901/2006 for Study BIA-2093-211, an open-label, 2-dose level trial to evaluate pharmacokinetics, safety, and tolerability of ESL as adjunctive therapy in infants with refractory epilepsy with partial-onset seizures aged from 1 month to <2 years.

Study BIA-2093-211/EXT is now totally completed with last patient completing the study (LPLV) on the 11th May 2021. The due date for submission of this CSR is 11th November 2021 (6 months from the completion of study). The CSR is dated 12 October 2021. Through the present application, the applicant is submitting to the EMA the results of this Clinical Study conducted in the paediatric population in accordance with Article 46 of Regulation (EC) No 1901/2006. A short critical expert overview has also been provided.

# 2. Scientific discussion

## *2.1. Information on the development program*

Study BIA-2093-211/EXT was a Phase 2, multinational, open-label extension of Study BIA-2093-211, which enrolled infants (≥1 month to <2 years) with refractory epilepsy who were experiencing POS.

## *2.2. Information on the pharmaceutical formulation used in the study*

The only investigational medicinal product tested in Study BIA-2093-211/EXT was ESL as an oral suspension (**Table 1**). As the medication is an oral suspension, bottles were to be shaken for approximately 1 minute on the occasion of the first use, confirming that no residues or powder were seen into the bottom or walls of the bottles.

**Table 1 Details of investigational medicinal product**

| | |
|---|---|
| Active substance | Eslicarbazepine acetate (ESL) |
| Trade name | None |
| Dosage form, strength | Oral suspension: 50 mg/mL |
| Presentation | Bottles containing 200 mL of oral suspension |
| Manufacturing site | BIAL - Portela & Cª, S.A., 4745-457 Coronado (S. Romão e S. Mamede), Portugal |
| Packaging/Labelling site | Theorem Clinical Research/Chiltern, Am Kronberger Hang 3 (Entrance C), 65824 Schwalbach am Taunus, Germany |

## *2.3. Clinical aspects*

### 2.3.1. Introduction

Eslicarbazepine acetate (ESL; BIA 2-093, Zebinix®) was developed by BIAL-Portela & Cª., S.A. (BIAL) as an antiepileptic drug (AED).

ESL is authorized as monotherapy in the treatment of partial-onset seizures (POS), with or without secondary generalisation, in adults with newly diagnosed epilepsy and as adjunctive therapy in adults, adolescents and children aged above 6 years, with POS with or without secondary generalisation. The clinical development of ESL for monotherapy in the paediatric population as well as adjunctive therapy is ongoing.

Zebinix is approved as immediate release tablets containing 200, 400, 600 and 800 mg of ESL and as an oral suspension (50 mg/mL).

Pursuant to Article 22 of Regulation (EC) No. 1901/2006 as amended, BIAL submitted to the EMA on 22 September 2014 an application for modification of the agreed paediatric investigation plan (PIP) with a deferral and a waiver as set out in the European Medicines Agency's (EMA)decision P/213/2011 issued on 2 September 2011, the decision P/0058/2012 issued on 26 March 2012, the decision P/0284/2012 issued on 23 November 2012 and the decision P/0197/2013 issued on 2 September 2013 and the decision P/0015/2015 issued on 30 January 2015. The last modification of the PIP (EMEA-000696-PIP02-10-M06) submitted on 21 March 2019 and was approved by EMA decision P/0272/2019 on 14 August 2019.

### 2.3.2. Clinical study

### BIA-2093-211/EXT

### Description

Study BIA-2093-211/EXT was a Phase 2, multinational, open-label extension of Study BIA-2093-211, which enrolled infants (≥1 month to <2 years) with refractory epilepsy who were experiencing POS.

The objective of the study was to assess the safety and tolerability of 1 year of treatment with ESL in the defined patient population and to perform exploratory analyses of efficacy. No primary or secondary objectives were defined for this study. All objectives were used to collect long-term data and were evaluated descriptively. Exploratory analysis of efficacy was assessed by evaluation of seizures (date, time, type, and duration) at each visit. Safety was assessed by monitoring/evaluation of treatment-emergent adverse events (TEAEs), physical and neurological examinations, vital signs, electrocardiograms (ECGs), and clinical safety laboratory tests at pre-specified time points (**Table 2**).

After completion of Study BIA-2093-211, parent(s) or guardian(s) could choose to allow their child to continue treatment with ESL for 1 year in Study BIA- 2093-211/EXT. During this 1-year study, subjects were grouped by treatment; age cohorts were not taken into consideration.

Up to 24 subjects will be enrolled in the extension study at an estimated 22 centres in approximately 12 to 13 countries in Europe (including Croatia, Czech Republic, Italy, Portugal, Romania, Russia, Serbia, and Ukraine). Other countries may be added as needed.

**Table 2 Objectives, endpoints, and statistical methods**

| Objectives | Endpoints | Statistical Analyses |
|---|---|---|
| To assess the safety and tolerability of 1 year of treatment with ESL in the defined patient population | TEAEs<br>Clinical laboratory endpoints: biochemistry and haematology<br>Urinalysis<br>Physical examinations<br>Neurological examinations<br>Vital signs<br>ECG | Continuous variables were summarised using descriptive statistics and categorical variables were summarised by frequency counts and percentages based on the Safety set.<br><br>Fisher's exact test was used to compare clinically significant laboratory values among dose groups |
| To perform exploratory analyses of efficacy | Seizures (date, time, type, and duration) recorded by the parent(s) or guardian(s) in the study diaries | Continuous data were summarised using descriptive statistics and categorical variables were summarised using frequency counts and percentages based on the Safety set. |

ECG = electrocardiogram; ESL = eslicarbazepine acetate; TEAE = treatment-emergent adverse event

## Methods

### *Study participants*

All 23 subjects who completed the BIA-2093-211 study continued in the BIA-2093-211/EXT study. Twelve subjects were enrolled in dose group ≤20 mg/kg/day, 7 subjects in dose group > 20 to ≤ 25 mg/kg/day, and 4 subjects in dose group >25 mg/kg/day. At the start of the BIA-2093-211, eight subjects were ≥1 to <6 months old, 5 subjects were ≥6 to <12 months old, and 10 subjects were ≥ 12 months old.

The majority of subjects completed this study, with similar percentages among the dose groups. Five (21.7%) subjects prematurely discontinued the study (3 subjects were ≥1 to <6 months old and 2 subjects were ≥12 months old at Visit 1 of BIA-2093-211); 1 of the 5 subjects (2 months old at Visit 1 of BIA-2093-211) in the >20 to ≤25 mg/kg/day dose group discontinued the study due to a serious adverse event (SAE) of seizure.

Baseline demographics were similar among the 3 dose groups. Similar proportions were male and female. Median height, weight, and body mass index were similar across dose groups. Median age was 5 months in the ≤ 20 mg/kg/day dose group, 19 months in the >20 to ≤25 mg/kg/day dose group, and 15.5 months in the >25 mg/kg/day dose group.

All subjects were white. Epilepsy history and baseline disease characteristics were collected in Study BIA-2093-211 and were consistent of a patient population with POS. The median age at onset and time since last seizure were similar among the dose groups. The number of total seizures prior to study entry increased from the lowest to the highest dose group. The proportion of subjects with complex partial seizures increased from the lowest to the highest dose group. At least 83.3% of subjects in any dose group had no family history of epilepsy.

***Treatments***

The mean treatment durations were 307.3, 347.6, and 374.3 days in ≤ 20 mg/kg/day, > 20 to ≤ 25 mg/kg/day, and >25 mg/kg/day dose groups, respectively. At least 75.0% of subjects in each dose group had a treatment duration of >40 weeks. The mean daily doses received were in accordance with the planned doses for each dose group :13.67, 20.58, and 24.95 mg/kg in the ≤20 mg/kg/day, > 20 to ≤ 25 mg/kg/day, and >25 mg/kg/day dose groups, respectively. The maximum dose allowed was 20 mg/kg/day for subjects ≥1 month to <6 months of age and 30 mg/kg/day for subjects ≥ 6 months to < 24 months of age. No subject was prescribed a daily dose higher than 30 mg/kg.

**Dosage schedule**

The treatment period was followed by a Down-titration Period for subjects on a dose of > 5 mg/kg/day at Week 52: for ESL doses of ≤20 mg/kg/day, down-titration occurred in 1 step, reducing the dose by half for a 5-day period; for ESL doses of >20 mg/kg/day, down-titration occurred in 2 steps, reducing the dose by half for each of two 5-day periods. The Down-titration Period was followed by a 4-week Follow-up Period after the last dose of study drug. The individual study duration was estimated to be between 56 and 58 weeks.

The study drug was ESL, an oral suspension of 50 mg/mL (batch numbers 160690, 180476, and 190412). Doses in each group were as follows:

| | **Study Period** | **Dose** |
|---|---|---|
| Dose Group ≤20 mg/kg/day | Treatment Period<br>Down-titration Period[a] (1 step of 5 days) | ≤20 mg/kg/day<br>Dose (QD) reduced by half |
| Dose Group >20 - ≤25 mg/kg/day | Treatment Period<br>Down-titration Period (2 steps of 5 days) | >20 - ≤25 mg/kg/day<br>Dose (QD) reduced by half at each step |
| Dose Group >25 mg/kg/day | Treatment Period<br>Down-titration Period (2 steps of 5 days) | >25 mg/kg/day<br>Dose (QD) reduced by half at each step |

QD = once daily.
[a] Down-titration Period applicable only for subjects on a dose >5 mg/kg/day.

## Results

***Efficacy results***

Efficacy will only be assessed descriptively in this study and will be based on details captured in the subject diaries for seizures (date, time, type, and duration). The parent(s) or guardian(s) of each subject will be instructed to record the number of seizures per day throughout the study. They will be required to indicate whether or not a seizure has occurred on each day. The subject diary will not be part of the CRF. The relevance of any observed differences must be considered in the context of the small sample size, different ESL treatment durations, as well as being an open-label study with no placebo control. High intra-subject variability in this paediatric population (1 month to <2 years) must

be considered as well, due to major physiological modifications occurring rapidly during the first 2 years of life. The study showed high inter-individual variability in the PK of eslicarbazepine in the different age groups.

During the Treatment Period, the median standardised seizure frequency (i.e. median number of seizures per week) decreased for all dose groups with the greatest decrease in the lowest dose group ( ≤ 20 mg/kg/day) and the lowest decrease in the highest dose group (> 25 mg/kg/day). On a percentage basis, the median relative percent change ranged from -86.01% in the lowest dose group ( ≤ 20 mg/kg/day) to -12.68% in the highest dose group (> 25 mg/kg/day). A similar pattern was observed during the Down-titration and Follow-up Periods. Of note, efficacy results in the highest dose group were not explored beyond the maximum daily dose allowed in the study (30 mg/kg/day). The reductions in seizure frequencies were similar between male and female subjects.

Among male subjects during the treatment period, the median relative change from baseline was similar among all dose groups ranging from -70.30% to -86.64% seizures per week compared with baseline. A similar pattern was observed among dose groups during the Down-titration and Follow-up Periods. A greater number of seizures per week relative to the Treatment and Follow-up Periods was observed during the Down-titration Period.

Among female subjects during the Treatment Period, the median relative change from baseline was similar among the 2 lowest dose groups ranging from -81.52% to -88.04%. With only 1 female subject in the highest dose group, the median relative change from baseline was 61.28%. A similar pattern was observed during the Downtitration and Follow-up Periods.

During the Treatment Period (up to 52 weeks duration), 1 subject was seizure free: a female subject in the ≤20 mg/kg/day dose group.

The most common seizure type reported during the study was complex partial, followed by partial evolving to secondarily generalized. Noteworthy reductions from baseline in standardized seizure frequency during the Treatment Period were primarily observed for complex partial and partial evolving to secondarily generalized types of seizures.

For complex partial seizures, median relative reductions from baseline during the Treatment Period were similar for all dose groups and ranged from -50.13 % to -86.34 % for all dose groups. For complex partial seizures, no notable differences were observed between male and female subjects in the relative change from baseline. For both sexes, the percentage reductions from baseline were similar among dose groups ranging from -50.13% to - 87.23% for male subjects and -53.66% to - 87.42% for female subjects.

For partial evolving to secondarily generalised type of seizures, none were observed at baseline in the highest > 25 mg/kg/day dose group but were observed in the other 2 dose groups. Mean standardised seizure frequency was 7.3 for the lowest dose and 39.7 for the mid dose (Table 3). During the Treatment Period, the median percentage reductions from baseline were similar for the 2 lowest dose groups ranging from -81.52% to -95.00%.

During the baseline period, simple partial seizures were only observed in the lowest dose group but were observed in all 3 dose groups during the treatment period and later periods. Therefore, relative changes from baseline cannot be calculated during subsequent periods of this trial for the 2 dose groups with 0 seizures during the baseline period. Median relative change from baseline in the lowest dose group was 12.15% during the Treatment Period, 55% during the Down-titration Period, and - 57.86% during the Follow-up Period. The median increases from baseline for simple partial seizures during the treatment period and Down-titration Period contrast with the median decreases from baseline observed for complex partial seizures.

**Table 3 Standardised Seizure Frequency and Change from Baseline by Gender and by Seizure Type and Study Period - Safety Set**

| | Statistic | Dose group | | |
|---|---|---|---|---|
| | | ≤20 mg/kg/day N=12 | >20–≤25 mg/kg/day N=7 | >25 mg/kg/day N=4 |
| Partial evolving to | n | 12 | 7 | 4 |
| secondarily generalised | Mean | 7.3 | 39.7 | 0.0 |
| | SD | 15.39 | 54.41 | 0.00 |
| | %CV | 209.84 | 137.01 | - |
| | Min | 0 | 0 | 0 |
| | Median | 0.0 | 0.0 | 0.0 |
| | Max | 54 | 131 | 0 |
| 0 | n (%) | 7 (58.3) | 4 (57.1) | 4 (100.0) |
| 1 | n (%) | 0 | 0 | 0 |
| 2 | n (%) | 0 | 0 | 0 |
| 3-5 | n (%) | 1 (8.3) | 0 | 0 |
| ≥6 | n (%) | 4 (33.3) | 3 (42.9) | 0 |

**Gender: Male**

| Seizure Type / Time-point / Parameter | Statistic | ≤20 mg/kg N=5 | >20 - ≤25 mg/kg N=4 | >25 mg/kg N=3 |
|---|---|---|---|---|
| Partial evolving to secondarily generalised | | | | |
| Baseline Period | | | | |
| Standardised seizure frequency (number of seizures per week) | n | 5 | 4 | 3 |
| | nmiss | 0 | 0 | 0 |
| | Mean | 2.40 | 7.25 | 0.00 |
| | SD | 3.362 | 9.142 | 0.000 |
| | %CV | 140.064 | 126.102 | - |
| | Min | 0.0 | 0.0 | 0.0 |
| | Median | 0.00 | 5.00 | 0.00 |
| | Max | 7.0 | 19.0 | 0.0 |

**Gender: Female**

| Seizure Type / Time-point / Parameter | Statistic | ≤20 mg/kg N=7 | >20 - ≤25 mg/kg N=3 | >25 mg/kg N=1 |
|---|---|---|---|---|
| Partial evolving to secondarily generalised | | | | |
| Baseline Period | | | | |
| Standardised seizure frequency (number of seizures per week) | n | 7 | 3 | 1 |
| | nmiss | 0 | 0 | 0 |
| | Mean | 2.43 | 15.00 | 0.00 |
| | SD | 4.791 | 25.981 | - |
| | %CV | 197.271 | 173.205 | - |
| | Min | 0.0 | 0.0 | 0.0 |
| | Median | 0.00 | 0.00 | 0.00 |
| | Max | 13.0 | 45.0 | 0.0 |

CV= coefficient of variation; Max = maximum; Min = minimum; N = number of subjects in the Safety set; n = number of subjects with data available; SD = standard deviation. %: Percentage is based on N. Information about the epilepsy related history was collected at Visit 1 in Study BIA-2093-211.

### *Safety results*

Nineteen subjects (82.6%) had ≥1 TEAE; 2 subjects had 6 severe TEAEs, all not related (wound infection, astrocytoma [low grade], akathisia, febrile convulsion [2 events in the same subject], and

seizure). One subject had a TEAE of seizure which was reported as an SAE and was considered possibly related to study drug which led to discontinuation. No subject had a TEAE leading to death.

The overall pattern of TEAEs reflected not only the known safety profile of ESL, but also the most common events occurring in the paediatric population with refractory epilepsy with POS. The most common system organ classes in which TEAEs were reported (≥3 subjects) were infections and infestations (15 subjects [65.2%]), investigations (7 subjects [30.4%]), nervous system disorders (7 subjects [30.4%]), gastrointestinal disorders (6 subjects [26.1%]), respiratory, thoracic and mediastinal disorders, and blood and lymphatic system disorders both with 3 subjects (13.0%).

The most common TEAEs (≥3 subjects) by preferred term were bronchitis (5 subjects [21.7%]), respiratory tract infection (4 subjects [17.4%]), and respiratory tract infection viral, somnolence, pharyngitis, and viral upper respiratory tract infection, all with 3 subjects (13.0%).

The most common treatment-related TEAE was somnolence, reported in 3 subjects (13.0%). All other related TEAEs were reported in single subjects (change in seizure presentation [severity reported as moderate], seizure [2 related TEAEs in 1 subject reported as moderate], tremor [moderate], alanine aminotransferase increased [mild], electrocardiogram PR prolongation [mild], atrioventricular block first degree [mild], overdose [mild], dermatitis allergic [2 TEAEs in 1 subject reported as mild], and hyponatraemia [mild].

Two subjects in the ≤ 20 mg/kg/day dose group had related TEAEs; 1 subject with somnolence and electrocardiogram PR prolongation, the other with hyponatraemia. One subject in the > 25 mg/kg/day dose group had a related TEAE of alanine aminotransferase increased, and all other related TEAEs were reported in the >20 to ≤25 mg/kg/day dose group.

Four subjects (17.4%) had 1 or more SAEs: 3 subjects (25%) in the ≤20 mg/kg/day dose group and 1 subject (14.3%) in the>20 to ≤25 mg/kg/day dose group. The 4 subjects had a total of 10 SAEs. The most common SAE was seizure, with 3 events reported in 2 subjects (8.7%). All other SAEs were reported in single subjects: akathisia, febrile convulsion (2 events in 1 subject), laryngitis, wound infection, exposure to toxic agent, and astrocytoma (low grade). Two of the SAEs were considered related to study drug: 2 events of seizure reported in the same subject.

No clinically meaningful changes over time were observed in haematology, urinalysis, or vital signs (mean systolic blood pressure, diastolic blood pressure, pulse rate, or body weight). One clinically significant event of low sodium was reported for 1 subject in the ≤20 mg/kg/day dose group at Visit 1 (sodium 127 mmol/L, normal range 131- 142 mmol/L). This event was reported as a TEAE of hyponatraemia (mild). The subject was excluded from study after Visit 1.

ESL did not cause a clinically relevant prolongation of the QT interval corrected for heart rate (QTc) at doses of 5, 10, and 20 mg/kg/day. The mean change from baseline in QT interval corrected for heart rate using Bazett's formula (ΔQTcB) values ranged between -17.7 and 19.5 ms. The mean absolute change from baseline in QT interval corrected for heart rate using Fridericia's formula (ΔQTcF) values ranged between -13.8 and 15.5 ms. No subject in any of the dose groups had a change from baseline QTcB or QTcF value greater than 60 ms.

No clinically significant changes were observed in heart rate (HR) or QRS (Time from the onset of the Q wave to the end of the S wave) duration in any dose group based on a by-time-point analysis. Categorical analysis revealed only few subjects with low heart rate (8 subjects), high PR interval (7 subjects), and high QRS duration values (4 subjects). Of these, the majority of the observed values were close to the threshold value of the age-dependent criteria.

One subject was reported with a TEAE of PR prolongation and 1 subject with atrioventricular block first degree. Both were non-serious, mild, and recovered without any change in the ESL dose. 3 types of

treatment-emergent morphological abnormalities were reported: sinus bradycardia, first degree atrioventricular block, and non-specific T wave abnormality. No treatment-emergent U wave changes were noted during the study. None of the subjects had arrhythmias like torsades de pointes, ventricular tachycardia, or ventricular fibrillation or flutter, which would suggest a potential pro-arrhythmic effect. For ECG findings, the proportions of subjects with abnormal ECG findings at postbaseline visits were similar to those reported at baseline. Physical and neurological examination findings that were normal or abnormal at baseline tended to stay normal or abnormal when evaluated at the endpoint visit.

### 2.3.3. Discussion on clinical aspects

PK, safety, and tolerability of ESL were characterised in an open-label Phase 2 study (BIA-2093-211) of infants from 1 month to <2 years old with refractory epilepsy and POS. No primary or secondary objectives were defined for this study. Safety and tolerability were assessed, and efficacy was evaluated with exploratory analyses based on the Safety set. All objectives were used to collect long-term data and were evaluated descriptively.

The overall pattern of TEAEs reflected not only the known safety profile of ESL, but also the most common events occurring in the paediatric population with refractory epilepsy with POS. The proportion of subjects with ≥1 TEAE was similar among the 3 dose groups considering the small sample size in the analysis, and no indication of a relationship with ESL dose was observed. Most TEAEs were assessed as mild or moderate in intensity. No subjects experienced a TEAE leading to death. Four subjects had 1 or more serious TEAEs, 1 of which led to discontinuation of study drug, which was primarily related to lack of efficacy as the subject's mother was concerned by her child's ongoing seizures. No clinically meaningful changes over time were observed in parameters for haematology, urinalysis, vital signs, ECGs, and physical and neurological examinations. The majority of TEAEs were considered unrelated to study drug.

Comparisons between dose groups are not meaningful because of the small numbers of subjects in each dose group. There was a high intra-subject variability in the paediatric population (1 month to <2 years) due to major physiological modifications occurring rapidly during the first 2 years of life.

The most common seizure type reported during the study extension was complex partial, followed by partial evolving to secondarily generalised. Substantial reductions from baseline in standardised seizure frequency during the treatment period were primarily observed for complex partial and partial evolving to secondarily generalised seizure types.

The median standardised seizure frequency (i.e. median number of seizures per week) decreased for all dose groups with the greatest decrease (- 86.01 %) observed in the lowest dose group ( ≤ 20 mg/kg/day), whereas in the highest dose group (> 25 mg/kg/day) the decrease of seizure frequency was - 12.68%. A similar pattern was observed during the Down-titration and Follow-up Periods. The reductions in seizure frequencies were similar between male and female subjects.

# 3. CHMP overall conclusion and recommendation

The relevance of any observed differences between dose groups in safety and efficacy results have to be considered in the context of the small sample size, different ESL treatment durations, and being an open-label study with no placebo control. Therefore, from the results of the extension of the open-label phase 2 study BIA-2093-211 no definite conclusions could be drawn regarding the optimal ESL dose.

In addition, the extension phase of the study does not yield any new efficacy aspects of ESL in children. There were also no new safety signals observed, and the safety profile reflected the known safety profile for ESL in children > 6 years old and in adults. The MAH does not propose any amendment of the product information and this is agreed.

## ☒ Fulfilled:

No regulatory action required.

# Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

## Non clinical studies

Product Name: Zebinix Active substance: eslicarbazepine acetate (ESL)

| Study title | Study number | Date of completion | Date of submission of final study report |
|---|---|---|---|
| Toxicity and toxicokinetic study of 28 days repeat doses of ESL in juvenile dogs | WIL-682001 | September 2009 | The report was included in the submission of paediatric indication (June 2015) |
| 10-month oral (gavage) toxicity study of ESL in juvenile dogs with a 2-month recovery period | WIL-682002 | April 2010 | The report was included in the submission of paediatric indication (June 2015) |

## Clinical studies

Product Name: Zebinix Active substance: eslicarbazepine acetate (ESL)

| Study title | Study number | Date of completion | Date of submission of final study report |
|---|---|---|---|
| Open-label, multiple dose study to evaluate pharmacokinetics, safety and tolerability of ESL for partial onset epilepsy in paediatric patients from 2 years to less than 18 years | BIA-2093-202 | April 2006 | The CSR was included in the initial MAA of Zebinix for adjunct therapy in adult population, in 2008 |
| Double-blind study in paediatric epileptic subjects aged from 5 to less than 8 years to compare the subject preference for ESL suspension formulation with alternative flavours | BIA-2093-212 | December 2012 | June 2013 |
| Double-blind, randomised, placebo controlled, parallel group, multicentre trial to evaluate efficacy and safety of ESL as adjunctive therapy for refractory partial seizures including effect on cognitive function of ESL as adjunctive therapy in children aged 6 years to less than 16 years with a one year open label extension phase | BIA-2093-208 | May 2013 (Part II)<br><br>(Part III) | December 2013 (The final study report includes Part I and Part II)<br><br>October 2015 |
| Double-blind, randomised, placebo controlled, parallel group, multicentre trial to evaluate efficacy and safety of ESL as adjunctive therapy for refractory partial seizures in children aged 2 years to less than 18 years with a one | BIA-2093-305 | October 2013 (Part II)<br><br>June 2014 (cut-off date for Asia) | April 2014 (The final study report includes Part I and Part II)<br><br>February 2015 (The study report includes Part III, IV and V from Europe and part III from Asia). |

| | | | |
|---|---|---|---|
| year open label extension phase | | August 2017 (Parts IV and V in Asia) | February 2018 (The study report includes Parts III to V from Asia) |
| Open-label, 2-dose level trial to evaluate pharmacokinetics, safety, and tolerability of ESL as adjunctive therapy in infants with refractory epilepsy with partial-onset seizures aged from 1 month to <2 years | BIA-2093-211 | April 2020 | October 2020 |
| Open-label, 2-dose level trial to evaluate pharmacokinetics, safety, and tolerability of ESL as adjunctive therapy in infants with refractory epilepsy with partial-onset seizures aged from 1 month to <2 years– 1-year extension | BIA-2093-211/EXT | May 2021 | October 2021 |